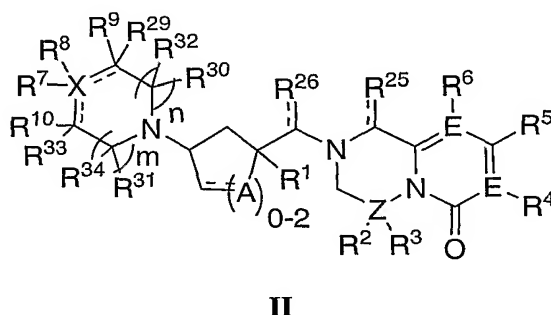
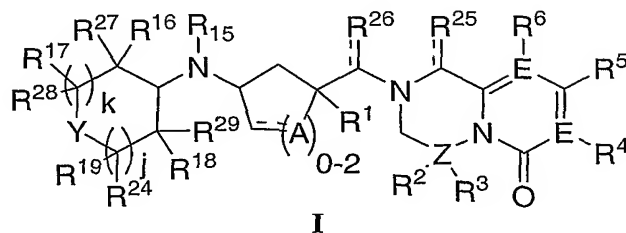


WHAT IS CLAIMED IS:

1. A compound of Formula I or Formula II:



wherein:

A is selected from: $-\text{CH}_2-$, $-\text{O}-$, $-\text{N}(\text{R}^{20})-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{N}(\text{SO}_2\text{R}^{14})-$, and $-\text{N}(\text{COR}^{13})-$;

E is independently selected from N and C;

X is O, N, S, SO_2 or C;

Y is selected from: $-\text{O}-$, $-\text{N}(\text{R}^{20})-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, and $-\text{C}(\text{R}^{21})(\text{R}^{22})-$, $-\text{N}(\text{SO}_2\text{R}^{14})-$, $-\text{N}(\text{COR}^{13})-$, $-\text{C}(\text{R}^{21})(\text{COR}^{11})-$, $-\text{C}(\text{R}^{21})(\text{OCOR}^{14})-$ and $-\text{CO}-$;

Z is selected from C, N or O;

R^1 is selected from: hydrogen, $-\text{C}_{1-6}\text{alkyl}$, $-\text{O}-\text{C}_{1-6}\text{alkyl}$, $-\text{S}-\text{C}_{1-6}\text{alkyl}$, $-\text{SO}-\text{C}_{1-6}\text{alkyl}$, $-\text{SO}_2-\text{C}_{1-6}\text{alkyl}$, $-\text{SO}_2\text{NR}^{12}\text{R}^{12}$, $-\text{NR}^{12}-\text{SO}_2-\text{NR}^{12}\text{R}^{12}$, $-(\text{C}_{0-6}\text{alkyl})-(\text{C}_{3-7}\text{cycloalkyl})-(\text{C}_{0-6}\text{alkyl})$, $-\text{CN}$, $-\text{NR}^{12}\text{R}^{12}$, $-\text{NR}^{12}\text{COR}^{13}$, $-\text{NR}^{12}\text{SO}_2\text{R}^{14}$, $-\text{COR}^{11}$, $-\text{CONR}^{12}\text{R}^{12}$, $-\text{NR}^{12}\text{CONR}^{12}\text{R}^{12}$, $-\text{O}-\text{CO}-\text{C}_{1-6}\text{alkyl}$, $-\text{O}-\text{CO}_2-\text{C}_{1-6}\text{alkyl}$, hydroxy, heterocycle and phenyl,

where said alkyl and cycloalkyl are unsubstituted or substituted with 1-7 substituents independently selected from: halo, hydroxy, -O-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -CONR¹²R¹², -NR¹²CONR¹²R¹², -COR¹¹, -SO₂R¹⁴, -NR¹²COR¹³, -NR¹²SO₂R¹⁴, -heterocycle, =O, -CN, phenyl, -SO₂NR¹²R¹², -NR¹²-SO₂-NR¹²R¹², -S-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -SO-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -SO₂-C₁₋₆alkyl, unsubstituted or substituted with 1-6 fluoro, and -O-COR¹³,

where said phenyl and heterocycle are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, -COR¹¹, C₁₋₃alkyl, and C₁₋₃alkoxy, said C₁₋₃alkyl and C₁₋₃alkoxy being unsubstituted or substituted with 1-6 fluoro;

R² and R³ are nothing when Z is O;

R² is nothing and R³ is hydrogen or C₁₋₃alkyl when Z is N;

R² and R³ are independently hydrogen or C₁₋₃alkyl unsubstituted or substituted with 1-3 fluoro, when Z is C;

R⁴ is selected from: hydrogen, C₁₋₃alkyl unsubstituted or substituted with 1-3 fluoro, -O-C₁₋₃alkyl unsubstituted or substituted with 1-3 fluoro, hydroxy, chloro, fluoro, bromo, phenyl and heterocycle, when E is C;

R⁵ is selected from: fluoro, chloro, bromo, -heterocycle, -CN, -COR¹¹, C₄₋₆cycloalkyl, -O-C₄₋₆cycloalkyl, C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro or hydroxyl or both, -O-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -CO-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -S-C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro, -pyridyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C₁₋₄alkyl and COR¹¹, -phenyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C₁₋₄alkyl and COR¹¹, -O-phenyl unsubstituted or substituted with one or more substituents selected from halo, trifluoromethyl, C₁₋

₄alkyl and COR¹¹, -C₃₋₆cycloalkyl unsubstituted or substituted with 1-6 fluoro, and -O-C₃₋₆cycloalkyl unsubstituted or substituted with 1-6 fluoro, when E is C;

R⁶ is selected from: hydrogen, hydroxy, chloro, fluoro, bromo, phenyl, heterocycle, C₁₋₃alkyl unsubstituted or substituted with 1-3 fluoro and -O-C₁₋₃alkyl unsubstituted or substituted with 1-3 fluoro, when E is C;

R⁴ and R⁶ are independantly selected from nothing or O (to make an N-oxide) when E is N;

R⁷ is selected from: hydrogen, (C₀₋₆alkyl)-phenyl, (C₀₋₆alkyl)-heterocycle, (C₀₋₆alkyl)-C₃₋₇cycloalkyl, (C₀₋₆alkyl)-COR¹¹, (C₀₋₆alkyl)-(alkene)-COR¹¹, (C₀₋₆alkyl)-SO₃H, (C₀₋₆alkyl)-W-C₀₋₄alkyl, (C₀₋₆alkyl)-CONR¹²-phenyl and (C₀₋₆alkyl)-CONR²³-V-COR¹¹, when X is N or C,

where W is selected from: a single bond, -O-, -S-, -SO-, -SO₂-, -CO-, -CO₂-, -CONR¹²- and -NR¹²-,

where V is selected from C₁₋₆alkyl or phenyl,

where R²³ is hydrogen or C₁₋₄alkyl, or R²³ is a 1-5 carbon linker to one of the carbons of V to form a ring,

where said C₀₋₆alkyl is unsubstituted or substituted with 1-5 substituents independently selected from: halo, hydroxy, -C₀₋₆alkyl, -O-C₁₋₃alkyl, trifluoromethyl and -C₀₋₂alkyl-phenyl,

where said phenyl, heterocycle, cycloalkyl and C₀₋₄alkyl, if present, are unsubstituted or substituted with 1-5 substituents independently selected from: halo, trifluoromethyl, hydroxy, C₁₋₃alkyl, -O-C₁₋₃alkyl, -C₀₋₃-COR¹¹, -CN, -NR¹²R¹², -CONR¹²R¹² and -C₀₋₃-heterocycle,

or where said phenyl or heterocycle is fused to another heterocycle, said other heterocycle being unsubstituted or substituted with 1-2 substituents independently selected from hydroxy, halo, -COR¹¹, and -C₁₋₃alkyl,

and where alkene is unsubstituted or substituted with 1-3 substituents which are independently selected from: halo, trifluoromethyl, C₁₋₃alkyl, phenyl and heterocycle;

5 R⁷ is absent when X is O, S, or SO₂;

R⁸ is selected from: hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, -COR¹¹, -CONR¹²R¹² and -CN, when X is C;

10 R⁸ is nothing, when X is O, S, SO₂ or N, or when a double bond joins the carbons to which R⁷ and R¹⁰ are attached;

or, R⁷ and R⁸ are joined to form a ring selected from: 1H-indene, 2,3-dihydro-1H-indene, 2,3-dihydro-benzofuran, 1,3-dihydro-isobenzofuran, 2,3-dihydro-benzothiofuran, 1,3-dihydro-isobenzothiofuran, 6H-cyclopenta[d]isoxazol-3-ol, cyclopentane and cyclohexane,

15

where said ring is unsubstituted or substituted with 1-5 substituents independently selected from:
halo, trifluoromethyl, hydroxy, C₁₋₃alkyl, -O-C₁₋₃alkyl, -C₀₋₃-COR¹¹, -CN, -NR¹²R¹²,
-CONR¹²R¹² and -C₀₋₃alkyl-heterocycle;

20

R⁹ and R¹⁰ are independently selected from: hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-COR¹¹, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, halo;

or R⁹ and R¹⁰ together are O, where O is connected to the ring via a double bond;

25

or, R⁷ and R⁹, or R⁸ and R¹⁰, are joined to form a fused ring which is phenyl or heterocycle, wherein said fused ring is unsubstituted or substituted with 1-7 substituents independently selected from: halo, trifluoromethyl, hydroxy, C₁₋₃alkyl, -O-C₁₋₃alkyl, -COR¹¹, -CN, -NR¹²R¹² and -CONR¹²R¹²;

30 R¹¹ is independently selected from: hydroxy, hydrogen, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl, C₃₋₆ cycloalkyl, where said alkyl, phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with

1-6 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl, and trifluoromethyl;

R¹² is selected from: hydrogen, C₁₋₆ alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl, where said alkyl, phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl, and trifluoromethyl;

or, when two separate R¹² groups reside on the same atom or adjacent atoms, said two R¹² groups are optionally connected via a C₁₋₇alkyl linker to form a 3 to 9 membered ring, said linker being unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl and trifluoromethyl;

R¹³ is selected from: hydrogen, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl, where said alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl and trifluoromethyl;

R¹⁴ is selected from: hydroxy, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl, where said alkyl, phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl and trifluoromethyl;

R¹⁵ is hydrogen or C₁₋₆alkyl, where said alkyl is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, -CO₂H, -CO₂C₁₋₆alkyl, and -O-C₁₋₃alkyl;

R¹⁶ is selected from: hydrogen, fluoro, C₃₋₆ cycloalkyl, -O-C₃₋₆cycloalkyl, hydroxy, -COR¹¹, -OCOR¹⁴, C₁₋₆alkyl unsubstituted or substituted with 1-6 substituents selected from fluoro, C₁₋₃alkoxy, hydroxyl and -COR¹¹, and -O-C₁₋₃alkyl unsubstituted or substituted with 1-3 fluoro;

or, R¹⁵ and R¹⁶ together are a C₂₋₄alkyl or a C₀₋₂alkyl-O-C₁₋₃alkyl, forming a ring where said ring has 5-7 members;

R¹⁷ is selected from: hydrogen, COR¹¹, hydroxy, -O-C₁₋₆alkyl unsubstituted or substituted with 1-6 substituents selected from fluoro, C₁₋₃alkoxy, hydroxy, and -COR¹¹ and C₁₋₆alkyl unsubstituted or substituted with 1-6 substituents selected from fluoro, C₁₋₃alkoxy, hydroxy, and -COR¹¹, or R¹⁷ is nothing if R²⁸ is connected to a ring carbon via a double bond;

or, R¹⁶ and R¹⁷ together are C₁₋₄alkyl or C₀₋₃alkyl-O-C₀₋₃alkyl, forming ring where said ring has 3-7 members;

R¹⁸ is selected from: hydrogen, fluoro, -O-C₃₋₆cycloalkyl, -O-C₁₋₃alkyl unsubstituted or substituted with 1-6 fluoro and C₁₋₆alkyl unsubstituted or substituted with 1-6 fluoro;

or, R¹⁶ and R¹⁸ together are C₂₋₃alkyl, where said alkyl is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, -COR¹¹, C₁₋₃alkyl, and C₁₋₃alkoxy;

or, R¹⁶ and R¹⁸ together are C₁₋₂alkyl-O-C₁₋₂alkyl, where said alkyl is unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, -COR¹¹, C₁₋₃alkyl, and C₁₋₃alkoxy;

or, R¹⁶ and R¹⁸ together are -O-C₁₋₂alkyl-O-, where said alkyl is unsubstituted or substituted with 1-3 substituents independently selected from halo, hydroxy, -COR¹¹, C₁₋₃alkyl, and C₁₋₃alkoxy;

R¹⁹ is selected from: hydrogen, COR¹¹, SO₂R¹⁴, SO₂NR¹²R¹² and C₁₋₃alkyl unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxyl;

R²⁰ is selected from: hydrogen, C₁₋₆ alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl, where said alkyl, phenyl, benzyl and cycloalkyl groups are unsubstituted or substituted with 1-6 substituents independently selected from halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl, and trifluoromethyl;

R²¹ and R²² are independently selected from: hydrogen, hydroxy, C₁₋₆ alkyl, -O-C₁₋₆alkyl, benzyl, phenyl and C₃₋₆ cycloalkyl where said alkyl, phenyl, benzyl, and cycloalkyl groups can be unsubstituted or substituted with 1-6 substituents independently selected from: halo, hydroxy, C₁₋₃alkyl, C₁₋₃alkoxy, -CO₂H, -CO₂-C₁₋₆ alkyl and trifluoromethyl;

5 R²⁴ is selected from: hydrogen, COR¹¹, SO₂R¹⁴, SO₂NR¹²R¹² and C₁₋₃alkyl, where said alkyl is unsubstituted or substituted with 1-6 substituents independently selected from: fluoro and hydroxyl;

or, R²⁴ and R¹⁷ together are a C₁₋₃alkyl bridge;

10 R²⁵ and R²⁶ are independently selected from: =O where R²⁵ and/or R²⁶ is oxygen and is connected via a double bond, hydrogen, phenyl, and C₁₋₆alkyl substituted or unsubstituted with 1-6 substituents selected from -COR¹¹, hydroxy, fluoro, chloro and C₁₋₃alkyl;

R²⁷ is selected from: hydrogen, COR¹¹, SO₂R¹⁴, SO₂NR¹²R¹² and C₁₋₃alkyl, where said alkyl is
15 unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxyl;

R²⁸ is selected from selected from: hydrogen, hydroxy, halo, C₁₋₃alkyl unsubstituted or substituted with 1-6 substituents independently selected from fluoro and hydroxy, -NR¹²R¹², -COR¹¹, -CONR¹²R¹², -NR¹²COR¹³, -OCONR¹²R¹², -NR¹²CONR¹²R¹², -heterocycle, -CN, -NR¹²-SO₂-NR¹²R¹², -NR¹²-
20 SO₂-R¹⁴, -SO₂-NR¹²R¹² and =O where R²⁸ is connected to the ring via a double bond and where R¹⁷ at the same position is absent;

R²⁹ and R³³ are selected from: hydrogen, hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-COR¹¹, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, trifluoromethyl and halo, or R²⁹ or R³³ are independently absent if the site of substitution is
25 unsaturated;

or, R²⁹ and R¹⁶ together are a C₁₋₃alkyl bridge;

R³⁰ and R³¹ are independently selected from: hydroxy, C₁₋₆alkyl, C₁₋₆alkyl-COR¹¹, C₁₋₆alkyl-hydroxy, -O-C₁₋₃alkyl, halo and hydrogen, where said alkyl are unsubstituted or substituted with 1-6 substituents independantly selected from fluoro and hydroxyl;
30

or, R^{30} and R^{31} together are a $-C_{1-4}alkyl-$, $-C_{0-2}alkyl-O-C_{1-3}alkyl-$ or $-C_{1-3}alkyl-O-C_{0-2}alkyl-$, where said alkyl are unsubstituted or substituted with 1-2 substituents consisting of oxy where the oxygen is joined to the bridge via a double bond, fluoro, hydroxy, methoxy, methyl or trifluoromethyl;

R^{32} and R^{34} are independently selected from: hydrogen, hydroxy, $C_{1-6}alkyl$, $C_{1-6}alkyl-COR^{11}$, $C_{1-6}alkyl-hydroxy$, $-O-C_{1-3}alkyl$, trifluoromethyl and halo;

j is 0, 1, or 2;

k is 0, 1, or 2;

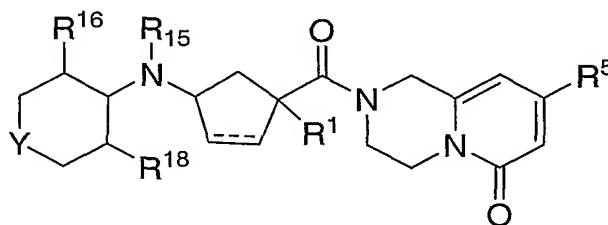
m is 0, 1, or 2;

n is 1 or 2;

the dashed line represents an optional single bond;

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

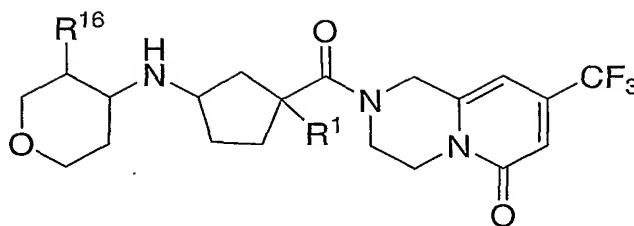
2. The compound of claim 1 of the Formula Ia:



Ia

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

3. The compound of claim 1 of the Formula Ib:

**Ib**

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

5

4. The compound of claim 1, wherein: A is CH₂, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

5. The compound of claim 1, wherein Y is O or CH₂, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

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6. The compound of claim 1, wherein E is C, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

7. The compound of claim 1, wherein Z is C, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

15

8. The compound of claim 1, wherein R¹ is selected from: -C₁₋₆alkyl, -C₀₋₆alkyl-O-C₁₋₆alkyl, heterocycle, and -(C₀₋₆alkyl)-(C₃₋₇cycloalkyl)-(C₀₋₆alkyl), where said alkyl, heterocycle and cycloalkyl are unsubstituted or substituted with 1-7 substituents independently selected from halo, hydroxy, -O-C₁₋₃alkyl, trifluoromethyl, C₁₋₃alkyl, -O-C₁₋₃alkyl, -COR¹¹, -CN, -NR¹²R¹², -CONR¹²R¹² and -NCOR¹³, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

20

9. The compound of claim 1, wherein R¹ is selected from: C₁₋₆alkyl, C₁₋₆alkyl substituted with hydroxy, and C₁₋₆alkyl substituted with 1-6 fluoro, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

25

10. The compound of claim 1, wherein R^1 is selected from: $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{OH})(\text{CH}_3)_2$, $-\text{CH}(\text{OH})\text{CH}_3$ and $-\text{CH}_2\text{CF}_3$, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

5 11. The compound of claim 1, wherein one or more of R^2 , R^3 and R^4 is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

12. The compound of claim 1, wherein R^5 is selected from: C_{1-6} alkyl substituted with 1-6 fluoro, $-\text{O}-\text{C}_{1-6}$ alkyl substituted with 1-6 fluoro, chloro, bromo and phenyl, and
10 pharmaceutically acceptable salts thereof and individual diastereomers thereof.

13. The compound of claim 12, wherein R^5 is trifluoromethyl, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

15 14. The compound of claim 1, wherein R^{15} is methyl or hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

15. The compound of claim 1, wherein R^{16} is selected from: hydrogen, C_{1-3} alkyl which is unsubstituted or substituted with 1-6 fluoro, $-\text{O}-\text{C}_{1-3}$ alkyl, fluoro and hydroxy, and
20 pharmaceutically acceptable salts thereof and individual diastereomers thereof.

16. The compound of claim 1, wherein R^{16} is selected from: hydrogen, trifluoromethyl, methyl, methoxy, ethoxy, ethyl, fluoro and hydroxy, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

25 17. The compound of claim 1, wherein R^{17} is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

18. The compound of claim 1, wherein R^{18} is selected from: hydrogen, methyl, and
30 methoxy, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

19. The compound of claim 1, R¹⁶ and R¹⁸ together are -CH₂CH₂- or -CH₂CH₂CH₂-, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

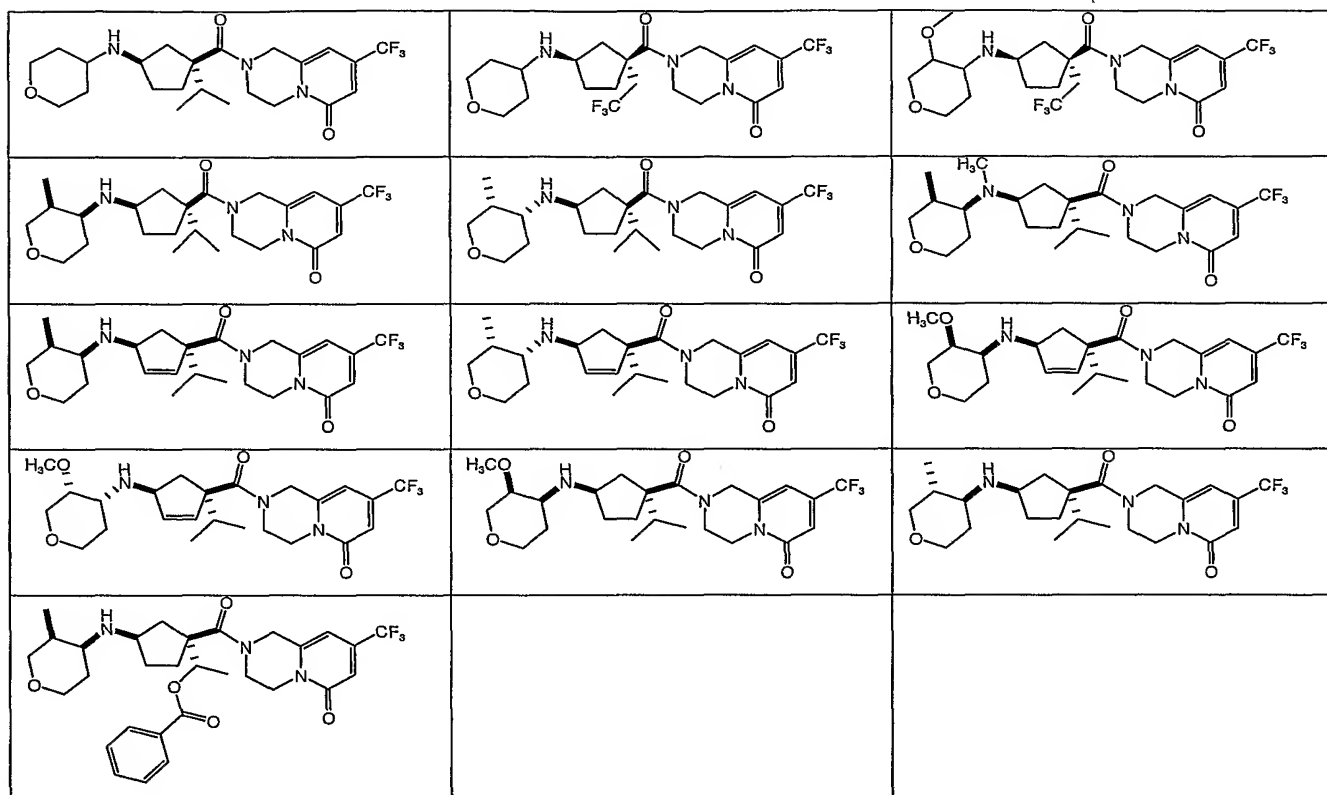
20. The compound of claim 1, wherein one or more of R¹⁹, R²⁴ and R²⁵ is hydrogen,
5 and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

21. The compound of claim 1, wherein R²⁶ is O, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

22. The compound of claim 1, wherein one or more of R^{27} , R^{28} and R^{29} is hydrogen, and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

23. A compound selected from:

5



and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

24. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

10

25. A method for modulations of chemokine receptor activity in a mammal which comprises the administration of an effective amount of a compound of Claim 1.

26. A method for treating, ameliorating, controlling or reducing the risk of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of a compound of Claim 1.

5 27. A method for treating, ameliorating, controlling or reducing the risk of rheumatoid arthritis which comprises the administration to a patient of an effective amount of a compound of Claim 1.